

216551

**NO DRAWINGS**

Priority Date(s): ..21.6.85.....  
.....  
Complete Specification Filed: 16.6.86..  
Class: .G07D233/.32,36,38;.....  
.G07155/.06; A61K31/415; A61K37/02..  
.....  
Publication Date: .....27 SEP 1989.....  
P.O. Journal, No: .....1324.....

N.Z. No.

NEW ZEALAND

Patents Act 1953

COMPLETE SPECIFICATION

PHARMACOLOGICALLY ACTIVE COMPOUNDS



We, I.S.F. S.p.A., an Italian company residing at Via  
Leonardo da Vinci 1, 20090 Trezzano Sul Naviglio (Milano),  
Italy,

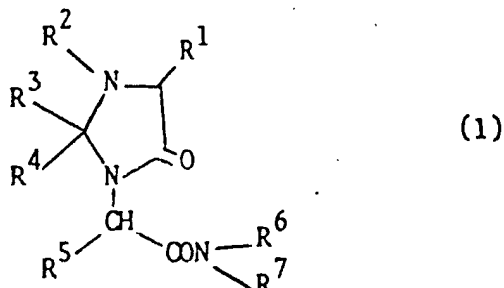
do hereby declare the invention, for which we pray that a  
Patent may be granted to us, and the method by which it is  
to be performed, to be particularly described in and by the  
following statement:-

PHARMACOLOGICALLY ACTIVE COMPOUNDS

This invention relates to new chemical compounds which have useful pharmacological activity, to processes and intermediates for making them, and pharmaceutical compositions containing them.

According to the invention we provide 5-oxo-1-imidazolidineacetamide derivatives of Structure (1)

10



15

in which

20

$R^1$  is H,  $C_{1-5}$  alkyl (straight or branched), or a phenyl or benzyl group optionally substituted by  $C_{1-5}$  alkyl (straight or branched),  $C_{1-4}$  alkoxy (straight or branched) or hydroxy;

25

$R^2$  is H, OH,  $C_{1-5}$  alkyl (straight or branched), aryl or acyl;

30

$R^3$  is H,  $C_{1-5}$  alkyl (straight or branched) or phenyl and  $R^4$  is  $C_{1-5}$  alkyl (straight or branched) or phenyl, or  $R^3$  and  $R^4$  can together form a 1,4-butylene or 1,5-pentylene group;

$R^5$  is H or  $C_{1-5}$  alkyl (straight or branched);

35

$R^6$  is H,  $C_{1-5}$  alkyl (straight or branched),  $-CHR^8CONH_2$  or  $-CHR^8CONHCHR^9CONH_2$ ; where  $R^8$  and  $R^9$  (which can be the same or different) are H or  $C_{1-5}$  alkyl (straight or branched); and

$R^7$  is H or  $C_{1-5}$  alkyl (straight or branched),

and pharmaceutically acceptable salts thereof.

5            Preferably  $R^1$  is H, methyl or isobutyl, particularly H.

Preferably  $R^2$  is H, formyl or acetyl.

10           Examples of aryl groups are phenyl, and naphthyl which may be optionally substituted by  $C_{1-5}$  alkyl (straight or branched),  $C_{1-4}$  alkoxy (straight or branched) or hydroxy. Preferably the aryl groups are phenyl, 4-hydroxyphenyl, and 4-methoxyphenyl. Examples  
15           of acyl groups are  $C_{1-5}$  (straight or branched) alkanoyl groups, particularly formyl, acetyl and propionyl, and aroyl groups, particularly benzoyl and substituted benzoyl groups such as 4-methoxybenzoyl.

20           Preferably  $R^3$  and  $R^4$  are both methyl or together form a 1,4-butylene or 1,5-pentylene group, or  $R^3$  is methyl or isopropyl and  $R^4$  is hydrogen.

25           Preferably  $R^5$  is H, methyl, isopropyl, 1-methyl-propyl or isobutyl.

Preferably  $R^6$  is H,  $-CHR^8CONH_2$  or  $-CHR^8CONHCHR^9CONH_2$ .

Preferably  $R^7$  is H.

30           Preferably  $R^8$  is H, methyl, isopropyl, 1-methyl-propyl or isobutyl.

35           Preferably  $R^9$  is H, methyl, isopropyl, 1-methyl-propyl or isobutyl.

It will be appreciated that there will be chiral centres present if  $R^1$  is other than hydrogen, if  $R^3$  and  $R^4$  are different, and if any of  $R^5$ ,  $R^8$  and  $R^9$  are other than hydrogen. The present invention includes all optical isomers of the compounds of Structure (1) in their resolved and partially resolved forms and in the forms of racemic mixtures. When the synthetic precursor for the substituent can be a natural amino acid then preferably that substituent will have the natural (L) configuration.

Particularly preferred compounds of Structure (1) are:

- 2,2-dimethyl-5-oxo-1-imidazolidineacetamide,
- 2-(1-methylethyl)-5-oxo-1-imidazolidineacetamide,
- 2-(2,2-dimethyl-5-oxo-1-imidazolidineacetamido)acetamide,
- 2-[2-(2,2-dimethyl-5-oxo-1-imidazolidineacetamido)acetamido]acetamide,
- 2,2,4-trimethyl-5-oxo-1-imidazolidineacetamide,
- 3-acetyl-2,2-dimethyl-5-oxo-1-imidazolidineacetamide,
- 3-formyl-2,2-dimethyl-5-oxo-1-imidazolidineacetamide,
- (S)-2-[2,2-dimethyl-4-isobutyl-5-oxo-1-imidazolidineacetamido]acetamide,
- 2-methyl-5-oxo-1-imidazolidineacetamide,
- 2-(2-isopropyl-5-oxo-1-imidazolidineacetamido)acetamide,
- and

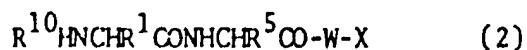
2-[4S-isobutyl]-2-isopropyl-5-oxo-1-imidazolidine-  
acetamido]acetamide,

and their pharmaceutically acceptable salts.

5

The compounds of Structure (1) can be prepared by  
reacting a compound of Structure (2)

10



15

in which  $R^{10}$  is H, OH,  $C_{1-5}$  alkyl (straight or  
branched) or aryl, W is a bond,  $-NHCHR^8CO-$  or  
 $-NHCHR^8CONHCHR^9CO-$ , and X is  $-NR^6R^7$  or  $-OH$  where  
 $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are as defined above provided  
that  $R^6$  and  $R^7$  are both hydrogen when W is other than  
a bond, with a carbonyl compound  $R^3COR^4$ , and when X  
is  $-OH$  the product is converted into the corresponding  
20 compound in which X is  $NR^6R^7$ , and when X is  $-OH$  and W  
is a bond or  $-NHCHR^8CO-$  the product is converted into a  
compound in which W is  $-NHCHR^8CO-$  or  $-NHCHR^8CONHCHR^9CO-$   
and X is  $-NR^6R^7$ , and when  $R^2$  in the product is  
hydrogen optionally the product is converted into a  
25 compound in which  $R^2$  is acyl, and optionally the  
compound of Structure (1) is converted into a  
pharmaceutically acceptable salt.

30

When  $R^3$  is H the carbonyl compound is an aldehyde  
and from equimolar to two molar equivalents of the  
aldehyde are used. When  $R^3$  is other than H the  
carbonyl compound is a ketone and preferably a larger  
excess of the ketone is used, together with higher  
temperatures and/or longer reaction times than for the  
35 corresponding reactions with aldehydes.

Conversion of a compound in which X is  $-OH$  into a  
compound in which X is  $-NR^6R^7$  requires the activation  
of the carboxyl group or the use of a peptide coupling

reagent. This procedure will necessitate the temporary protection of the secondary amino groups in compounds in which  $R^2$  is H. Suitable methods for activating carboxyl groups, suitable peptide coupling reagents and protecting groups are all well known to the art and are described for example in 'Peptide Synthesis' by M. Bodansky, Y Klausner and M. Ondetti (Wiley, 1976) and in 'Protective Groups in Organic Synthesis' by T.W. Greene (Wiley, 1981). Examples of activated derivatives of carboxyl groups are acyl chlorides, acyl azides, mixed anhydrides (e.g. formed with an alkyl chloroformate or pivaloyl chloride) and activated esters (e.g. trichlorophenyl, N-hydroxysuccinimido and 1-hydroxybenzotriazole esters). Examples of peptide coupling reagents are carbodiimides and Woodward's Reagent K (N-ethyl-5-phenylisoxazolium-3'-sulphonate). Examples of nitrogen-protecting groups are benzyloxycarbonyl and t-butyloxycarbonyl.

When the peptide side chain contains chiral centres (i.e. when  $R^5$ ,  $R^8$  and  $R^9$  are other than hydrogen) then the route of synthesis and the reagents will be chosen to ensure that only a small degree of racemisation occurs under the reaction conditions. When racemisation is not a problem and  $R^6$  is a mono-peptide or dipeptide unit the preferred synthesis is that in which W is a bond and the mono-peptide or dipeptide unit is incorporated at a later stage.

The compounds of Structure (1) have useful nootropic activity, that is they help restore learning and memory difficulties associated with ageing and various pathologies including Alzheimer's disease. To evaluate the nootropic activity, the compounds were submitted to pharmacological tests designed to detect a positive action on cognitive processes disrupted by an experimental cerebral impairment.

In particular the protection against the amnesia induced by maximal electroconvulsive shock (ECS) was studied. The experimental procedure described by Banfi et al., J. Pharmacol. Methods, 8 ; 255-264 (1982) was followed: Male albino CD Swiss mice from Charles River (Calco, Italy) are used. Mice were 35 days old. The apparatus is essentially the same as described by Essman [Pharm. Res. Commun., 5, 295-302, (1973)]. The passage from a light box (10x10x12 cm) into a dark one (23x16x12 cm) was punished by unavoidable foot shocks (0.3mA, 50Hz, 5 sec). In order to erase newly encoded information in the memory, a maximal ECS (30 mA, 150 msec, 50 Hz) is given to the mice by corneal electrodes immediately after the trial. The retest is performed 24 hr after ECS. Mice that did not cross from the light box into the dark one in 60 sec were considered as not affected by the retrograde amnesic effect of ECS. Groups of control animals were submitted to sham ECS to demonstrate the amnesic action of ECS. Saline or tested compounds are injected i.p. to groups of at least 20 mice 1 hr before the conditioning trial. The number of animals showing retention over the total number in each treated group is compared with that of controls by the chi square test.

25

The compounds under study are tested at the doses of 0.3 mg/kg, 1 mg/kg, 10 mg/kg and 30 mg/kg. The difference in percentage retention between the control saline-treated mice submitted to ECS and those submitted to sham ECS demonstrated the amnesic action of ECS. The degree of protective activity of the compounds is evaluated by comparing the groups treated with the compounds plus ECS to the group treated with saline alone plus ECS. Significant protective action was observed, for example, after intraperitoneal administration of 2-(1-methylethyl)-5-oxo-1-imidazolidineacetamide or

35

2-(2,2-dimethyl-5-oxo-1-imidazolidineacetamido)acetamide  
in a dose range from 0.3 to 30 mg/kg.

The specific mechanism of action of the compounds  
5 can be characterised by high affinity choline uptake  
determinations using synaptosomal preparations from  
cortical and hippocampal rat tissues, for example as  
described by F. Pedata et al., Clinical Neuropharmacology,  
7, (Suppl. 1), 772-3, (1984). Activity in this test  
10 indicates that the compounds might enhance cholinergic  
neurotransmission by increasing the amount of choline  
pre-synaptically available which in turn would lead to an  
increase in brain acetylcholine levels, thus improving  
the performance of brains in which choline and  
15 acetylcholine levels were abnormally low.

An alternative method for investigating the  
selective action of the compounds of Structure (1) is to  
test their activity in rats against both the disruptive  
20 action of scopolamine on mnestic trace and on the  
reduction of acetylcholine levels in hippocampus.

In order to use a compound of Structure (1) for the  
therapeutic treatment of humans and animals, it is  
25 normally formulated in accordance with standard  
pharmaceutical practice as a pharmaceutical composition.  
Therefore in another aspect the present invention  
provides a pharmaceutical composition which comprises a  
compound of Structure (1) and a pharmaceutically  
30 acceptable carrier.

The compounds of the Structure (1) may be  
administered in standard manner for the treatment of the  
indicated diseases, for example orally, parenterally,  
35 rectally, transdermally or via trans-mucosal (for example  
sub-lingual, or buccal or insufflatory) administration.



The compounds of the Structure (1) which are active when given orally or via sub-lingual or buccal administration can be formulated as syrups, tablets, capsules and lozenges. A syrup formulation will generally consist of a suspension or solution of the compound or salt in a liquid carrier for example, ethanol, glycerine or water with a flavouring or colouring agent. Where the composition is in the form of a tablet, any pharmaceutical carrier routinely used for preparing solid formulations may be used. Examples of such carriers include magnesium stearate, starch, lactose and sucrose. Where the composition is in the form of a capsule, any routine encapsulation is suitable, for example using the aforementioned carriers in a hard gelatin capsule shell. Where the composition is in the form of a soft gelatin shell capsule any pharmaceutical carrier routinely used for preparing dispersions or suspensions may be utilised, for example aqueous gums, celluloses, silicates or oils and are incorporated in a soft gelatin capsule shell.

Typical parenteral compositions consist of a solution or suspension of the compound of the Structure (1) in a sterile aqueous or non-aqueous carrier optionally containing a parenterally acceptable oil, for example polyethylene glycol, polyvinylpyrrolidone, lecithin, arachis oil, or sesame oil.

A typical suppository formulation comprises a compound of Structure (1) which is active when administered in this way, with a binding and/or lubricating agent, for example polymeric glycols, gelatins, cocoa-butter or other low melting vegetable waxes or fats.

157-50  
216551

Typical transdermal formulations comprise a conventional aqueous or non-aqueous vehicle, for example a cream, ointment, lotion or paste or can be in the form of a medicated plaster, patch or membrane.

5

Preferably the composition is in unit dosage form, for example a tablet or capsule, so that the patient may administer to himself a single dose.

10

Piracetam is a compound which is used in the treatment of senile dementia and related disease conditions. The compounds of Structure (1) can be administered in similar regimes to those established for piracetam with any appropriate adjustment in dose levels or frequency of dosing having regard to the greater activity and better pharmacological profile of the compounds of Structure (1).

15

Each dosage unit for oral administration contains suitably from 0.5 mg/Kg to 50 mg/Kg, and preferably from 1 mg/Kg to 8 mg/Kg, and each dosage unit for parenteral administration contains suitably from 0.1 mg/Kg to 10 mg/Kg, of a compound of Structure (1).

20

The daily dosage regimen for oral administration is suitably about 0.5 mg/Kg to 100 mg/Kg, more suitably about 1 mg/Kg to 25 mg/Kg of a compound of Structure (1) calculated as the free base. The active ingredient may be administered from 1 to 6 times daily. The compounds of Structure (1) may be co-administered with other pharmaceutically active compounds, for example in combination, concurrently or sequentially, particularly with other compounds used in the treatment of elderly patients e.g. tranquillisers, diuretics antihypertensives, vasodilator and inotropic agents.

25

30

35

The invention is illustrated by the following Examples.

2,2-Dimethyl-5-oxo-1-imidazolidineacetamide

- 5     A.    1)    To an ice cold solution of thionyl chloride  
            (5 ml) in dry ethanol (50 ml) a solution of sodium  
            2,2-dimethyl-5-oxo-1-imidazolidineacetate (4g) in  
            dry ethanol (50 ml) was added dropwise. The mixture  
            was stirred at 0°C for 1 hour, then at room  
10            temperature overnight. After evaporation under  
            reduced pressure, the residue was taken up with a  
            saturated solution of sodium hydrogen carbonate and  
            extracted with 3x100 ml of dichloromethane. The  
            organic layer was dried and evaporated, to yield  
15            ethyl 2,2-dimethyl-5-oxo-1-imidazolidineacetate  
            (2.57g) as a colorless oil (Rf. 0.49, methanol/  
            acetone 1:1; silica gel plates). Oxalate salt  
            m.p. 109-113°C (ethanol/diethyl ether).
- 20            2)    An ice cold solution of ethyl 2,2-dimethyl-5-  
            oxo-1-imidazolidineacetate (2 g) in methanol  
            (150 ml) was saturated with gaseous ammonia. The  
            solution was stirred at room temperature for  
            36 hours. After evaporation, the residue was  
25            chromatographed on a silica gel column, eluting with  
            dichloromethane/methanol 6:4. The selected fractions  
            were collected, evaporated and the residue was  
            crystallized from ethanol, to give 1 g of the title  
            compound, as a white powder, m.p. 144-146°C.
- 30            B)            To a solution of glycylglycinamide acetate  
                          (10 g) in methanol (250 ml) and acetone (125 ml),  
                          was added Amberlite IRA-68 resin (20 g). Amberlite  
                          is a registered trade mark and IRA-68 is a weakly  
35            basic resin. The suspension was stirred at room  
            temperature for 1 hour, then resin was filtered off

216551

and the solution was evaporated under reduced pressure. The residue was suspended in refluxing acetone (250 ml) and methanol was added to obtain a clear solution, which was refluxed for 2 hours.

5 Evaporation and titration of the residue with acetone gave 6.85 g of the title compound.

Example 2

10 1) To 50 ml of anhydrous ethanol stirred at 0-5°C, 2 ml thionyl chloride were added. At the same temperature 2.1 g (0.01 mol) of sodium 2-(1-methylethyl)-5-oxo-1-imidazolidineacetate were added. The suspension obtained was stirred at 0°C for 1 hour and at room temperature

15 for 2 hours. The solvent was evaporated under reduced pressure and the residue taken up with ethyl acetate. The solid residue was filtered off and the solvent evaporated. The residue was dissolved in a saturated solution of sodium hydrogen carbonate and extracted with 3x50 ml

20 of dichloromethane. The organic layers were dried and evaporated to give ethyl 2-(1-methylethyl)-5-oxo-1-imidazolidineacetate (0.9 g) as a pale-yellow oil (42%) (Rf 0.6; ethyl acetate/dichloromethane 6:4; silica gel plates). Hydrochloride salt, m.p. 148-149°C

25 (methanol/ethyl acetate).

2) An ice cold solution of 3.8 g (0.018 mol) of ethyl 2-(1-methylethyl)-5-oxo-1-imidazolidineacetate in 100 ml of methanol was saturated with gaseous ammonia.

30 The solution was stirred at room temperature overnight and the solvent was evaporated under reduced pressure, to give 2-(1-methylethyl)-5-oxo-1-imidazolidineacetamide (3.4 g) as a viscous oil (Rf 0.33; ethyl acetate/methanol 6:4; silica gel plates). Monohydrate of sulphate salt

35 m.p. 64°C resolidifying with final decomposition at 114-118°C.

Example 32-(2,2-Dimethyl-5-oxo-1-imidazolidineacetamido)acetamide

To a solution of glycylglycylglycinamide acetate  
5 (800 mg) in methanol (8 ml) and acetone (15 ml),  
Amberlite IRA-68 resin (2 ml) was added. The suspension  
was stirred at room temperature for 1 hour, then the  
resin was filtered off and the solution was evaporated  
under reduced pressure. The residue was suspended in  
10 acetone and stirred at room temperature overnight. The  
precipitate was collected and crystallized from ethyl  
acetate, to give the title compound, as a white powder,  
m.p. 102-105°C dec.

15 Example 42-[2-(2,2-Dimethyl-5-oxo-1-imidazolidineacetamido)  
acetamido]acetamide

The same procedure of the Example 3 starting from  
20 triglycylglycinamide acetate afforded the title compound  
as a white powder, Rf 0.2 (dichloromethane/methanol 1:1;  
silica gel plates), m.p. 100-105°C dec.

Example 525 2,2,4-Trimethyl-5-oxo-1-imidazolidineacetamide

The same procedure of the Example 3 starting from  
alanylglycinamide acetate afforded the title compound as  
a white hygroscopic solid, Rf 0.48 (dichloromethane/  
30 methanol 1:1; silica gel plates). Maleate salt, m.p.  
142-144°C dec.

Example 63-Acetyl-2,2-dimethyl-5-oxo-1-imidazolidineacetamide

35 A solution of 2,2 dimethyl-5-oxo-1-imidazolidine-  
acetamide (1.7 g) in acetic anhydride (9 ml) was stirred  
at 70-80°C for 5 minutes. The precipitate was collected

and washed with acetone, affording the title compound as a white powder, m.p. 188-189°C (ethyl acetate).

Example 7

5 3-Formyl-2,2-dimethyl-5-oxo-1-imidazolidineacetamide

The same procedure of Example 6, using mixed acetic-formic anhydride yielded the title compound as a white powder m.p. 211-213°.

10

Example 8

(S)-2-[2,2-Dimethyl-4-isobutyl-5-oxo-1-imidazolidine acetamido]acetamide

15 The same procedure of Example 3 starting from L-leucylglycylglycinamide hydrochloride, afforded the title compound as a white hygroscopic solid (Rf 0.47 dichloromethane-methanol 7:3, silica gel plates).

20

Example 9

2-Methyl-5-oxo-1-imidazolidineacetamide

A solution of glycylglycinamide (0.5g) and acetaldehyde (0.4 ml) in methanol (5 ml) was stirred at  
25 room temperature for 8 hours. Evaporation of the solvent gave a residue which was chromatographed on a silica gel column (eluant dichloromethane/methanol 75:25). The selected fractions were collected, evaporated to give the title compound (Rf = 0.3, dichloromethane/methanol 7:3, silica gel plates). Mass spectrum (E.I., 70 eV, 1.5 mA),  
30 m/z = 142 ( $M^+ - CH_3$ ), 99.

Example 10

2-(2-Isopropyl-5-oxo-1-imidazolidineacetamido)acetamide

35

The same procedure of example 9, starting from glycylglycylglycinamide and isobutyraldehyde, afforded

the title compound as a white hygroscopic solid, m.p. 65-70°C. Mass spectrum (E.I., 70 eV, 1.5 mA),  $m/z = 199$  ( $M^+ - C_3H_7$ ).

5

Example 11

2-[4S-Isobutyl-2-isopropyl-5-oxo-1-imidazolidine-acetamido]acetamide

10

The same procedure of example 9, starting from L-leucylglycylglycinamide and isobutyraldehyde, afforded the title compound as a diastereoisomeric mixture, Rf 0.58 (dichloromethane-methanol 7:3) Mass spectrum (E.I., 70 eV, 1.5 mA),  $m/z = 255$  ( $M^+ - C_3H_7$ ).

15

Example 12

Composition for 1 tablet

	2-(1-methylethyl)-5-oxo-1-imidazolidine-acetamide	100	mg
20	lactose	100	mg
	corn starch	80	mg
	talcum	11.5	mg
	silicon dioxide	4	mg
	magnesium stearate	2.5	mg
25	gelatine	2.0	mg

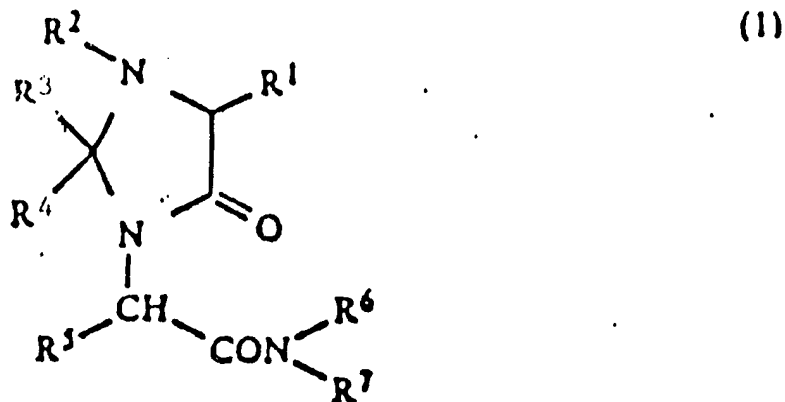
30

For the manufacture of 1000 tablets, 100 g of active ingredient are mixed with 100 g of lactose and 70 g of corn starch. The mixture is moistened with an aqueous solution of gelatine and then granulated and dried. The granules are mixed with 10 g of corn starch, 11.5 g of talcum, 4.0 g of silicon dioxide and 2.5 g of magnesium stearate and the mixture is pressed into tablets each weighing 300 mg and having the active ingredient content of 100 mg. The tablets can have different shapes and breaking notches for finer adjustment of the dosage.

35

## WHAT WE CLAIM IS:

1. A compound of Structure (1)



wherein

$R^1$  is H,  $C_{1-5}$  alkyl (straight or branched), or a phenyl or benzyl group optionally substituted by  $C_{1-5}$  alkyl (straight or branched),  $C_{1-4}$  alkoxy (straight or branched) or hydroxy;

$R^2$  is H, OH,  $C_{1-5}$  alkyl (straight or branched), phenyl or naphthyl optionally substituted by  $C_{1-5}$  alkyl (straight or branched),  $C_{1-4}$  alkoxy (straight or branched), or hydroxy or  $C_{1-5}$  alkanoyl (straight or branched), benzoyl, or 4-methoxybenzoyl;

$R^3$  is H,  $C_{1-5}$  alkyl (straight or branched) or phenyl and  $R^4$  is  $C_{1-5}$  alkyl (straight or branched) or phenyl, or  $R^3$  and  $R^4$  can together form a 1,4-butylene or 1,5-pentylene group, with the proviso that when  $R^3$  is H,  $R^4$  is  $C_{2-5}$  alkyl (straight or branched);

$R^5$  is H or  $C_{1-5}$  alkyl (straight or branched);

$R^6$  is H,  $C_{1-5}$  alkyl (straight or branched),  $-CHR^8CONH_2$  or

$CHR^8CONHCHR^9CONH_2$ ; where  $R^8$  and  $R^9$  (which can be the same or different) are H or  $C_{1-5}$  alkyl (straight or branched); and

$R^7$  is H or  $C_{1-5}$  alkyl (straight or branched), or a pharmaceutically acceptable salt thereof.





SECRET

716551

2. A compound according to Claim 1 in which  $R^1$  is H, methyl or isobutyl.

5 3. A compound according to Claim 1 or Claim 2 in which  $R^2$  is H, formyl or acetyl.

10 4. A compound according to any one of Claims 1 to 3 in which  $R^3$  and  $R^4$  are both methyl or together form a 1,4-butylene or 1,5-pentylene group, or  $R^3$  is hydrogen and  $R^4$  is isopropyl, or  $R^3$  is hydrogen and  $R^4$  is methyl.

15 5. A compound according to any one of Claims 1 to 4 in which  $R^5$  is H, methyl, isopropyl, 1-methylpropyl or isobutyl.

6. A compound according to any one of Claims 1 to 5 in which  $R^6$  is H,  $-\text{CHR}^8\text{CONH}_2$  or  $-\text{CHR}^8\text{CONHCHR}^9\text{CONH}_2$ .

20 7. A compound according to any one of Claims 1 to 6 in which  $R^7$  is H.

25 8. A compound according to any one of Claims 1 to 7 in which  $R^8$  is H, methyl, isopropyl, 1-methylpropyl or isobutyl.

30 9. A compound according to any one of Claims 1 to 8 in which  $R^9$  is H, methyl, isopropyl, 1-methylpropyl or isobutyl.

35 10. A compound according to Claim 1 which is  
2-(1-methylethyl)-5-oxo-1-imidazolidineacetamide, or  
2-(2,2-dimethyl-5-oxo-1-imidazolidineacetamido)acetamide.

11. A compound according to Claim 1 selected from the group

2,2-dimethyl-5-oxo-1-imidazolidineacetamide,

5

2-[2-(2,2-dimethyl-5-oxo-1-imidazolidineacetamido)acetamido]acetamide,

2,2,4-trimethyl-5-oxo-1-imidazolidineacetamide,

10

3-acetyl-2,2-dimethyl-5-oxo-1-imidazolidineacetamide,

3-formyl-2,2-dimethyl-5-oxo-1-imidazolidineacetamide,

15 (S)-2-[2,2-dimethyl-4-isobutyl-5-oxo-1-imidazolidineacetamido]acetamide,

2-methyl-5-oxo-1-imidazolidineacetamide,

20 2-(2-isopropyl-5-oxo-1-imidazolidineacetamido)acetamide,  
and

2-[4S-isobutyl-2-isopropyl-5-oxo-1-imidazolidineacetamido]acetamide.

25

12. A pharmaceutical composition comprising a compound according to any one of Claims 1 to 11 and a pharmaceutical carrier.

30 13. A compound according to any one of Claims 1 to 11 suitable for use as a therapeutic agent.

14. A process for preparing a compound according to Claim 1 which comprises reacting a compound of Structure  
35 (2)



in which  $R^{10}$  is H, OH,  $C_{1-5}$  alkyl (straight or branched) or aryl, W is a bond,  $-NHCHR^8CO-$  or  $-NHCHR^8CONHCHR^9CO-$ , and X is  $-NR^6R^7$  or  $-OH$  where  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are as defined in any one of  
5 Claims 1 to 9 provided that  $R^6$  and  $R^7$  are both hydrogen when W is other than a bond; with a carbonyl compound  $R^3COR^4$ ; and

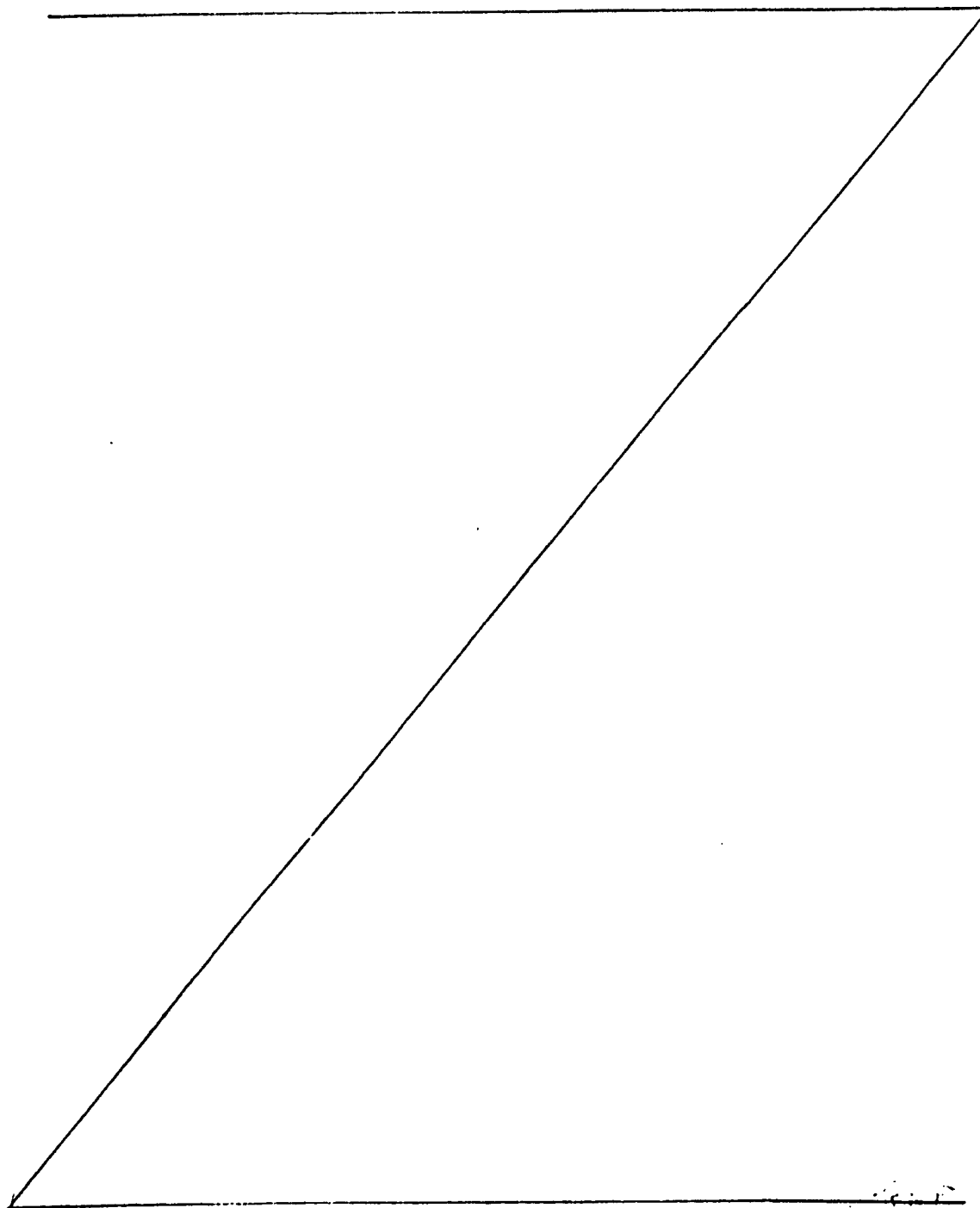
10 i) when X is  $-OH$  converting the product into the corresponding compound in which X is  $NR^6R^7$ ;

15 ii) when X is  $-OH$  and W is a bond or  $-NHCHR^8CO-$  converting the product into a compound in which W is  $-NHCHR^8CO-$  or  $-NHCHR^8CONHCHR^9CO-$  and X is  $-NR^6R^7$ ;

iii) when  $R^2$  is hydrogen optionally converting the product into a compound in which  $R^2$  is acyl;

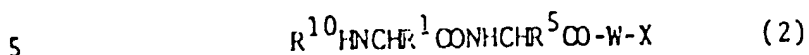
20 iv) optionally forming a pharmaceutically acceptable salt.

15. A process for preparing a compound of Structure  
(1) according to claim 1



22  
22  
28 AUG 1989

which comprises reacting a compound of Structure (2)



10 in which  $R^{10}$  is H, OH,  $C_{1-5}$  alkyl (straight or branched) or aryl, W is a bond,  $-NHCHR^8CO-$  or  $-NHCHR^8CONHCHR^9CO-$ , and X is  $-NR^6R^7$  or  $-OH$  where  $R^6$ ,  $R^7$ ,  $R^8$  and  $R^9$  are as defined in any one of Claims 1 to 9 provided that  $R^6$  and  $R^7$  are both hydrogen when W is other than a bond; with a carbonyl compound  $R^3COR^4$ ; and

15 i) when X is  $-OH$  converting the product into the corresponding compound in which X is  $NR^6R^7$ ;

20 ii) when X is  $-OH$  and W is a bond or  $-NHCHR^8CO-$  converting the product into a compound in which W is  $-NHCHR^8CO-$  or  $-NHCHR^8CONHCHR^9CO-$  and X is  $-NR^6R^7$ ;

25 iii) when  $R^2$  is hydrogen optionally converting the product into a compound in which  $R^2$  is acyl;

iv) optionally forming a pharmaceutically acceptable salt.

30 16. A process according to Claim 15 in which  $R^1$  is H, methyl or isobutyl.

17. A process according to Claim 15 or Claim 16 in which  $R^2$  is H, formyl or acetyl.



18. A process according to any one of Claims 15 to 17 in which  $R^3$  and  $R^4$  are both methyl or together form a 1,4-butylene or 1,5-pentylene group, or  $R^3$  is hydrogen and  $R^4$  is isopropyl, or  $R^3$  is hydrogen and  $R^4$  is methyl.

5

19. A process according to any one of Claims 15 to 18 in which  $R^5$  is H, methyl, isopropyl, 1-methylpropyl or isobutyl.

10

20. A process according to any one of Claims 15 to 19 in which  $R^6$  is H,  $-\text{CHR}^8\text{CONH}_2$  or  $-\text{CHR}^8\text{CONHCHR}^9\text{CONH}_2$ .

21. A process according to any one of Claims 15 to 20 in which  $R^7$  is H.

15

22. A process according to any one of Claims 15 to 21 in which  $R^8$  is H, methyl, isopropyl, 1-methylpropyl or isobutyl.

20

23. A process according to any one of Claims 15 to 22 in which  $R^9$  is H, methyl, isopropyl, 1-methylpropyl or isobutyl.

25

24. A process according to claim 15 in which the compound of Structure (1) is

2-(1-methylethyl)-5-oxo-1-imidazolidineacetamide, or

2-(2,2-dimethyl-5-oxo-1-imidazolidineacetamido)acetamide.

30

25. A process according to claim 15 in which the compound of Structure (1) is

2,2-dimethyl-5-oxo-1-imidazolidineacetamide,

35

2-[2-(2,2-dimethyl-5-oxo-1-imidazolidineacetamido)acetamido]acetamide,

- 2,2,4-trimethyl-5-oxo-1-imidazolidineacetamide,
- 3-acetyl-2,2-dimethyl-5-oxo-1-imidazolidineacetamide,
- 5 3-formyl-2,2-dimethyl-5-oxo-1-imidazolidineacetamide,
- (S)-2-[2,2-dimethyl-4-isobutyl-5-oxo-1-imidazolidine  
acetamido]acetamide,
- 10 2-methyl-5-oxo-1-imidazolidineacetamide,
- 2-(2-isopropyl-5-oxo-1-imidazolidineacetamido)acetamide,  
and
- 15 2-[4S-isobutyl-2-isopropyl-5-oxo-1-imidazolidine-  
acetamido]acetamide.

26. A process for preparing a pharmaceutical  
composition which comprises bringing into association a  
20 compound of Structure (1) in claim 15 and a pharmaceutical  
carrier.

27. A process according to claim 26 in which the  
compound of Structure (1) is  
25 2-(1-methylethyl)-5-oxo-1-imidazolidineacetamide, or  
2-(2,2-dimethyl-5-oxo-1-imidazolidineacetamido)acetamide.

28. A compound according to claim 1 substantially  
as herein described.

29. A process according to claim 15 substantially  
as herein described.



I.S.F. S.p.A.

100100 4072  
LIMITED,

*Roach*